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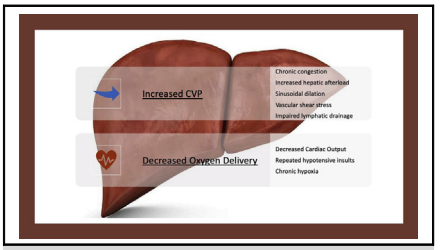
Commentary: Hepatocellular carcinoma: A threat for patients with Fontan circulation

Juan Contreras, MD,[a] and
David Faraoni, MD, PhD, FAHA[b]



Mechanisms promoting liver injury and fibrosis in Fontan-associated liver disease.

CENTRAL MESSAGE

Hepatocellular carcinoma has a low prevalence in Fontan patients, but it is a serious and potentially lethal complication. Further efforts are needed to systematize risk stratification and screening.

Since the first Fontan operation was performed in 1968, several modifications have been introduced that led to improvement in short- and long-term survival. The current 30-year survival after Fontan completion is 85%.[1,2] Hemodynamic changes associated with the Fontan circulation, including elevated central venous pressure and diminished cardiac output, as well as chronic hypoxic injury of the liver, are responsible for the development of Fontan-associated liver disease (FALD).[1] In Fontan circulation, the hepatic veins discharge directly into the Fontan circuit and the liver is therefore particularly susceptible to the effects of central venous hypertension. The elevated central venous pressure produces a centrilobular hepatic congestion and necrosis, and activation of inflammatory mediators that perpetuate the chronic inflammation and subsequent fibrosis of the liver.[3,4] The pathophysiological mechanisms promoting liver injury and fibrosis in FALD are summarized in Figure 1.

Histological studies suggest that 43% of patients with Fontan circulation have evidence of advanced liver fibrosis 30 years after the Fontan completion.[5] Liver fibrosis appears to be an inevitable complication in the Fontan circulation and the degree of fibrosis is increasing over time. In a retrospective study of Fontan patients receiving surveillance for FALD, 62% had evidence of chronic liver disease.[6] Among patients with liver cirrhosis, longitudinal studies suggest an annual risk of hepatocellular carcinoma (HCC) of 1% to 8%.[7] HCC is considered the most extreme manifestation of FALD. Most patients are asymptomatic and the diagnosis is usually incidental. The prognosis of HCC is very poor with survival rates estimated at 50% within 2 years of diagnosis.[8,9]

Wilson and colleagues[10] describe a low prevalence (5 of 1620 patients) of HCC from the Australian and New Zealand Fontan Registry, which is among the largest series of Fontan patients with excellent short- and long-term outcomes. All patients in the registry who develop HCC had evidence of cirrhosis, portal hypertension, and history of failing Fontan circulation.

Although the reported prevalence of HCC in patients with Fontan circulation is low, there is currently no consensus on the optimal timing to initiate screening and imaging in post-Fontan populations. Patients with failing Fontan, portal hypertension, or evidence of liver cirrhosis are at higher risk of HCC. Surveillance for HCC includes serum tests (eg, total and direct bilirubin, aminotransaminases, alkaline phosphatase, gamma-glutamyl transferase, albumin, and international normalized ratio) and imaging. Post-Fontan patients with a confirmed diagnosis of cirrhosis should undergo more rigorous screening. Follow-up in these patients should include ultrasound and alpha-fetoprotein measurement. Immunization against hepatitis

From the [a]Department of Cardiovascular Surgery and [b]Division of Cardiac Anesthesia, Department of Anesthesiology and Pain Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

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Address for reprints: David Faraoni, MD, PhD, FAHA, Division of Cardiac Anesthesia, Department of Anesthesiology and Pain Medicine, Hospital for Sick Children, 555 University Ave, Black Wing 2nd Floor, Room 2420, Toronto, Ontario M5G 1X8 Canada (E-mail: david.faraoni@sickkids.ca).

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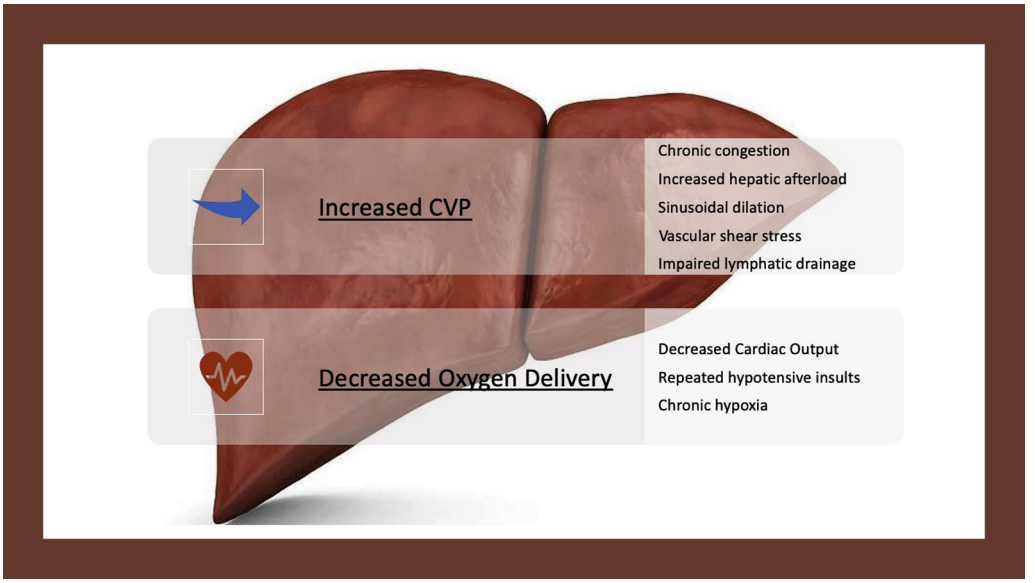

FIGURE 1. Mechanisms promoting liver injury and fibrosis in Fontan-associated liver disease.

A, hepatitis B, pneumococcal pneumonia, and influenza is also recommended. The use of pharmacologic agents such as pulmonary vasodilators (eg, sildenafil and bonsentan) and antifibrotic therapies could be considered to prevent the progression of FALD, although the effect on hepatic vascular resistance and on the prevalence of HCC is unknown and remains to be studied.[4] Further efforts are needed to systematize risk stratification and screening guidelines in patients with FALD.

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